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☐ 1. Document ID: US 6210666 B1

L3: Entry 1 of 5 File: USPT Apr 3, 2001

US-PAT-NO: 6210666
DOCUMENT-IDENTIFIER: US 6210666 B1

TITLE: Truncated .alpha.-galactosidase A to treat fabry disease

DATE-ISSUED: April 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miyamura; Nobuhiro	Kumamoto			JPX

US-CL-CURRENT: 424/94.61; 435/200, 435/208, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6177447 B1

L3: Entry 2 of 5 File: USPT Jan 23, 2001

US-PAT-NO: 6177447
DOCUMENT-IDENTIFIER: US 6177447 B1

TITLE: Deoxynojirimycin derivatives and their uses as glucosylceramidase inhibitors

DATE-ISSUED: January 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aerts; Johannes Maria F. G.	Abcoude			NLX
Pandit; Upendra Kumar	Amsterdam			NLX
Koomen; Gerrit-Jan	Heiloo			NLX
Overkleeft; Herman Steven	Leiden			NLX
Vianello; Paola	San Bovio			ITX

US-CL-CURRENT: 514/319; 546/195

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 5911983 A

L3: Entry 3 of 5 File: USPT Jun 15, 1999

US-PAT-NO: 5911983
DOCUMENT-IDENTIFIER: US 5911983 A

TITLE: Gene therapy for Gaucher disease using retroviral vectors

DATE-ISSUED: June 15, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barranger; John A.	Gibsonia	PA		
Robbins; Paul	Pittsburgh	PA		
Bahnson; Alfred B.	Pittsburgh	PA		

US-CL-CURRENT: 424/93.21; 424/93.6, 435/320.1, 435/372

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 5549892 A

L3: Entry 4 of 5 File: USPT Aug 27, 1996

US-PAT-NO: 5549892
DOCUMENT-IDENTIFIER: US 5549892 A

TITLE: Enhanced in vivo uptake of glucocerebrosidase

DATE-ISSUED: August 27, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; BethAnn	Arlington	MA		
Hayes; Michael	Acton	MA		

US-CL-CURRENT: 424/94.61; 435/209, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 5. Document ID: CA 2339888 A1, WO 9007573 A, EP 401362 A, CA 2006709 A, JP 03503721 W, US 5236838 A, EP 401362 A4, EP 401362 B1, DE 68926569 E, ES 2093642 T3, JP 2893481 B2

L3: Entry 5 of 5 File: DWPI Jun 23, 1990

DERWENT-ACC-NO: 1990-239045
DERWENT-WEEK: 200134

TITLE: Enzymatically active recombinant glucocerebrosidase - useful for treating Gauchers disease

INVENTOR: BARSOMIAN, G; BERGH, M ; RASMUSSEN, J

PRIORITY-DATA: 1988US-0289589 (December 23, 1988), 1989US-0455507 (December 22, 1989), 1989WO-US05801 (December 22, 1989), 1991US-0748283 (August 21, 1991)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
CA 2339888 A1	June 23, 1990	E	000	C12N005/10
WO 9007573 A	July 12, 1990		000	
EP 401362 A	December 12, 1990		000	
CA 2006709 A	July 31, 1990		000	
JP 03503721 W	August 22, 1991		000	
US 5236838 A	August 17, 1993		021	C12N009/42
EP 401362 A4	September 11, 1991		000	
EP 401362 B1	May 29, 1996	E	021	C12N009/24
DE 68926569 E	July 4, 1996		000	C12N009/24
ES 2093642 T3	January 1, 1997		000	C12N009/24
JP 2893481 B2	May 24, 1999		019	C12N015/09

INT-CL (IPC): A01K 67/00; C12N 5/00; C12N 5/10; C12N 9/24; C12N 9/42; C12N 15/09; C12N 15/52; C12N 15/56; C12N 15/63; C12N 15/79; C12N 15/81; C12N 15/85

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L3: Entry 1 of 5 File: USPT Apr 3, 2001

US-PAT-NO: 6210666
DOCUMENT-IDENTIFIER: US 6210666 B1

TITLE: Truncated .alpha.-galactosidase A to treat fabry disease

DATE-ISSUED: April 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miyamura; Nobuhiro	Kumamoto			JPX

US-CL-CURRENT: 424/94.61; 435/200, 435/208, 530/350

CLAIMS:

What is claimed is:
1. An isolated, purified .alpha.-galactosidase A polypeptide, or a variant thereof, which has a carboxy-terminal deletion of 2-11 amino acid residues and which exhibits .alpha.-galactosidase A enzyme activity.
2. The polypeptide of claim 1 corresponding to SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 or SEQ ID NO: 10.
3. A therapeutic method, comprising: administering to a human at risk of, or afflicted with, Fabry disease a therapeutically amount of the polypeptide of claim 1.
4. A therapeutic method, comprising: administering to a human at risk of, or afflicted with, a condition associated with a deficiency of .alpha.-galactosidase A a therapeutically effect amount of the polypeptide of claim 1.

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L3: Entry 1 of 5 File: USPT Apr 3, 2001

US-PAT-NO: 6210666
DOCUMENT-IDENTIFIER: US 6210666 B1

TITLE: Truncated .alpha.-galactosidase A to treat fabry disease

DATE-ISSUED: April 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miyamura; Nobuhiro	Kumamoto			JPX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Orphan Medical, Inc.	Minnetonka	MN			02

APPL-NO: 9/ 176666
DATE FILED: October 21, 1998

PARENT-CASE:
This application claims the benefit under 35 U.S.C. .sctn. 119 (e) of U.S. Provisional Application No. 60/062,560 filed on Oct. 21, 1997, which is hereby incorporated by reference.

INT-CL: [7] A61K 38/47, C12N 9/40
US-CL-ISSUED: 424/94.61; 435/200, 435/208, 530/350
US-CL-CURRENT: 424/94.61; 435/200, 435/208, 530/350
FIELD-OF-SEARCH: 435/200, 435/208, 530/350, 424/94.61

PRIOR-ART-DISCLOSED:

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Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4497797	February 1985	Ebata et al.	424/118
☐	5179023	January 1993	Calhoun et al.	435/320.1
☐	5356804	October 1994	Desnick et al.	435/208
☐	5401650	March 1995	Desnick et al.	435/208
☐	5658567	August 1997	Calhoun et al.	424/94.61

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Hantzopoulos, P.A., et al., "Expression of the Human .alpha.-Galactosidase A in Escherichia Coli K-12", Gene, 57, 159-169, (1987).
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ART-UNIT: 162
PRIMARY-EXAMINER: Prouty; Rebecca E.

ASSISTANT-EXAMINER: Hutson; Richard
ATTY-AGENT-FIRM: Schwegman, Lundberg, Woessner & Kluth, P.A.

ABSTRACT:

Fabry disease results from an X-linked deficiency in the enzyme .alpha.-galactosidase A. The present invention is directed to recombinant truncated forms of .alpha.-galactosidase A, as well as therapeutic compositions comprising said truncated .alpha.-galactosidase A which are useful, for example, to treat Fabry disease patients.

4 Claims, 13 Drawing figures

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L3: Entry 2 of 5 File: USPT Jan 23, 2001

US-PAT-NO: 6177447
DOCUMENT-IDENTIFIER: US 6177447 B1

TITLE: Deoxynojirimycin derivatives and their uses as glucosylceramidase inhibitors

DATE-ISSUED: January 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aerts; Johannes Maria F. G.	Abcoude			NLX
Pandit; Upendra Kumar	Amsterdam			NLX
Koomen; Gerrit-Jan	Heiloo			NLX
Overkleeft; Herman Steven	Leiden			NLX
Vianello; Paola	San Bovio			ITX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Universiteit van Amsterdam				NLX	03

APPL-NO: 9/ 230005
DATE FILED: April 30, 1999

PARENT-CASE:
This application is filed under 35 U.S.C. .sctn. 371 as a nation phase application of PCT application number PCT/NL97/00411 filed on Jul. 14, 1997.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
EP	96202010	July 15, 1996

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/NL97/00411	July 14, 1997	WO98/02161	Jan 22, 1998	Apr 30, 1999	Apr 30, 1999

INT-CL: [7] C07D 211/46, A61K 31/445
US-CL-ISSUED: 514/319; 546/195
US-CL-CURRENT: 514/319; 546/195
FIELD-OF-SEARCH: 546/192, 546/195, 514/317, 514/319

PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0022192A1	June 1980	EPX	
0034784A1	February 1981	EPX	
0193770A2	February 1986	EPX	
0305012A2	May 1989	EPX	
02306962	December 1990	EPX	
0477160A1	September 1991	EPX	
3024901A1	January 1982	NLX	
WO9413311	June 1994	WOX	
WO9522975	August 1995	WOX	
WO9502161	January 1998	WOX	

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Aerts et al, Molecular and Biochemical Abnormalities of Gaucher Disease: Chitotriosidase, a Newly Identified Biochemical Marker, Seminars of Hamatology, vol. 32, No. 3, pp. 16-13, 1995.
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PCT Notification of Transmittal of the International Preliminary Examination Report, 1999.
Hollak et al, Rapid Publication "Marked Elevation of Plasma Chitotriosidase Activity" A Novel Hallmark of Gaucher Disease, J. of Clinical Investigation, v. 93, pp. 1288-1292, Mar. 1994.

ART-UNIT: 165
PRIMARY-EXAMINER: Davis; Zinna Northington
ATTY-AGENT-FIRM: Cooper & Dunham LLP

ABSTRACT:

Deoxynojirimycin derivatives containing a large hydrophobic moiety, such as cholesterol or adamantame-methanol, linked through a spacer, such as pentamethylene, to the nitrogen atom of deoxynojirimycin, and salts thereof, inhibit glucosylceramidase and may be useful in the treatment of diseases involving a ceramide-mediated signaling process, such as Gaucher disease.

7 Claims, 4 Drawing figures

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L3: Entry 2 of 5 File: USPT Jan 23, 2001

US-PAT-NO: 6177447
DOCUMENT-IDENTIFIER: US 6177447 B1

TITLE: Deoxynojirimycin derivatives and their uses as glucosylceramidase inhibitors

DATE-ISSUED: January 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aerts; Johannes Maria F. G.	Abcoude			NLX
Pandit; Upendra Kumar	Amsterdam			NLX
Koomen; Gerrit-Jan	Heiloo			NLX
Overkleeft; Herman Steven	Leiden			NLX
Vianello; Paola	San Bovio			ITX

US-CL-CURRENT: 514/319; 546/195

CLAIMS:

What is claimed is:
1. Deoxynojirimycin compound containing a hydrophobic moiety linked through a spacer to the nitrogen atom of deoxynojirimycin, and salts thereof, wherein the spacer comprises an alkoxy polyalkylene or polyalkylene chain of from 3 to 8 carbon atoms and the hydrophobic moiety is a polycyclic alcohol group containing three or more rings that each share two or more carbon atoms with another ring and is capable of inserting in lipid bilayers.
2. A deoxynojirimycin compound according to claim 1 wherein the spacer comprises a polyalkylene chain of from 3 to 6 carbon atoms.
3. A deoxynojirimycin compound according to claim 1 wherein the spacer is a group having the structure --(CH.sub.2).sub.n -- wherein n is an integer from 3 to 8.
4. A deoxynojirimycin compound according to claim 1 wherein the hydrophobic moiety is derived from adamantanementhanol, cholesterol, .beta.-cholestanol, or 9-hydroxyphenanthrene.
5. A deoxynojirimycin compound according to claim 2 wherein the spacer is a polyalkylene chain having 5 carbon atoms.
6. Pharmaceutical composition comprising a deoxynojirimycin compound according to claim 1 and a pharmaceutically acceptable carrier.
7. A method of treatment of an individual suffering from Gaucher Fabry, Tay Sachs, Sandhoff or Niemann-Pick diseases, comprising administering to said individual an effective amount of a deoxynojirimycin derivative according to claim 1, optionally in combination with an effective amount of native or recombinant, modified or unmodified glucocerebrosidase.

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L3: Entry 2 of 5 File: USPT Jan 23, 2001

DOCUMENT-IDENTIFIER: US 6177447 B1
TITLE: Deoxynojirimycin derivatives and their uses as glucosylceramidase inhibitors

BSPR:
For more than thirty years supplementation of macrophages of Gaucher patients with human glucocerebrosidase has been seriously considered as a therapeutic option. Efforts to develop a therapy for Gaucher disease have been largely unsuccessful for many years due to the unavailability of sufficient amounts of pure human glucocerebrosidase and the poor targeting of intravenously administered enzyme to lysosomes of tissue macrophages. Only since 1990 an effective therapeutic intervention for Gaucher disease is available that is based on the chronic supplementation of patients with human glucocerebrosidase [8]. Administered by intravenous infusion is a human glucocerebrosidase that is modified in its N-linked glycans such that mannose-residues are terminally exposed. The modification favours uptake via mannose receptors. Improved targeting of the modified (`mannose-terminated`) enzyme to lysosomes of tissue macrophages occurs via mannose-receptor mediated endocytosis. Different dosing regimens that vary with respect to total dose (15-240 U/kg body weight.month) and frequency of administration (three times weekly to biweekly) are presently used (see e.g. ref. 9). Glucocerebrosidase isolated from human placenta (Ceredase; alglucerase) and enzyme recombinantly produced in CHO-cells (Cerezyme; imiglucerase) have been found to be equally potent in reversing some of the clinical signs associated with the disease [10].

DEPU:
10. Grabowski, G. A., Barton, N. W., Pastores, G., Dambrosia, J. M., Banerjee, T. K., McKee, M. A., Parker, C., Schiffmann, R., Hill, S. C., Brady, R. O. (1995) Ann. Int. Medicine 122, 33-39. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources.

WEST

Generate Collection

L3: Entry 3 of 5 File: USPT Jun 15, 1999

US-PAT-NO: 5911983
DOCUMENT-IDENTIFIER: US 5911983 A

TITLE: Gene therapy for Gaucher disease using retroviral vectors

DATE-ISSUED: June 15, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barranger; John A.	Gibsonia	PA		
Robbins; Paul	Pittsburgh	PA		
Bahnson; Alfred B.	Pittsburgh	PA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
University of Pittsburgh	Pittsburgh	PA			02

APPL-NO: 8/ 466597
DATE FILED: June 6, 1995

PARENT-CASE:
SPECIFICATION This application is a continuation-in-part of our application Ser. No. 07/904,809, filed Jun. 26, 1992, now abandoned. This invention was made with funding from the U.S. Government, which has certain rights therein.

INT-CL: [6] A61K 48/00, C12N 5/10, C12N 15/86
US-CL-ISSUED: 424/93.21; 424/93.6, 435/320.1, 435/372
US-CL-CURRENT: 424/93.21; 424/93.6, 435/320.1, 435/372
FIELD-OF-SEARCH: 435/69.1, 435/172.1, 435/172.3, 435/320.1, 435/240.2, 435/366, 435/372, 435/372.2, 435/372.3, 424/93.6, 424/93.2, 424/93.21

PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO9207943	May 1992	WOX	

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Barranger, J.A., N. Eng. J. Med. 311:1629-1631 (1984).
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ART-UNIT: 185
PRIMARY-EXAMINER: Guzo; David
ATTY-AGENT-FIRM: Baker & Botts, LLP

ABSTRACT:

The present invention relates to gene therapy for Gaucher disease using retroviral vectors which express the glucocerebrosidase gene. Methods are provided for transduction of autologous hematopoietic stem cells (e.g., human CD34+ cells) with these vectors and for transplantation of the transduced cells into a Gaucher disease patient to provide therapeutically effective levels of glucocerebrosidase activity. The invention also provides for retroviral vectors that express the glucocerebrosidase gene, and for human hematopoietic cells that contain the retroviral vector.

22 Claims, 46 Drawing figures

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L3: Entry 3 of 5 File: USPT Jun 15, 1999

US-PAT-NO: 5911983
DOCUMENT-IDENTIFIER: US 5911983 A

TITLE: Gene therapy for Gaucher disease using retroviral vectors

DATE-ISSUED: June 15, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barranger; John A.	Gibsonia	PA		
Robbins; Paul	Pittsburgh	PA		
Bahnson; Alfred B.	Pittsburgh	PA		

US-CL-CURRENT: 424/93.21; 424/93.6, 435/320.1, 435/372

CLAIMS:

We claim:
1. A human hematopoietic progenitor cell transduced with a retroviral vector, said vector comprising and expressing a DNA molecule that codes for glucocerebrosidase, wherein the transduced cell provides individual with Gaucher disease biologically active glucocerebrosidase.
2. The human hematopoietic cell of claim 1, wherein said cell is a hematopoietic stem cell.
3. The cells of claim 1, wherein the retroviral vector is R-GC.
4. The cells of claim 1, wherein the retroviral vector is MFG-GC.
5. The vector of claim 1, wherein the vector is R-GC.
6. The vector of claim 1, wherein the vector is MFG-GC, as deposited with the American Type Culture Collection and assigned accession number 75,733.
7. The cells of claim 2, wherein the cells are human CD34+ cells.
8. The cells of claim 2, wherein the retroviral vector is R-GC.
9. The cells of claim 2, wherein the retroviral vector is MFG-GC.
10. The cells of claim 7, wherein the retroviral vector is R-GC.
11. The cells of claim 7, wherein the retroviral vector is MFG-GC.
12. A retroviral vector selected from the group consisting of R-GC and MFG-GC.
13. A method for providing biologically active glucocerebrosidase to the cell of an individual with Gaucher disease, comprising:
a) isolating autologous bone marrow from the individual with Gaucher disease;
b) enriching the autologous bone marrow for hemapoietic progenitor cells to obtain an enriched hematopoietic progenitor cell population;
c) transducing the enriched progenitor cell population with a retroviral vector that contains and expresses the glucocerebrosidase gene; and
d) transplanting the transduced autologous progenitor cell population into the individual with Gaucher disease so as to provide to the individual biologically active glucocerebrosidase.
14. The method of claim 13, in which the hematopoietic progenitor cells are human CD34+ cells.
15. The method of claim 13, in which the retroviral vector is R-GC.
16. The method of claim 13, in which the retroviral vector is MFG-GC.
17. The method of claim 14, in which the retroviral vector is R-GC.
18. The method of claim 14, in which the retroviral vector is MFG-GC.
19. A method for providing biologically active glucocerebrosidase to the cells of an individual with Gaucher disease, comprising:

introducing an enriched bone marrow hematopoietic progenitor cell population into a Gaucher individual, said progenitor cell population having been treated in vitro to insert therein a DNA molecule encoding human glucocerebrosidase protein, said hematopoietic progenitor cell population expressing in said Gaucher individual biologically active glucocerebrosidase protein.

20. The method of claim 19, in which the enriched bone marrow hemapoietic progenitor cell population comprises human CD34+ cells.

21. The method of claim 13, wherein the transducing step is performed by centrifuging the hematopoietic progenitor cells with a retroviral containing supernatant.

22. The method of claim 19, wherein the DNA molecule encoding human glucocerebrosidase is inserted into the hematopoietic progenitor cell population by centrifuging the hematopoietic progenitor cells with a retroviral containing supernatant so as to effect transduction of the cell population.

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End of Result Set

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L3: Entry 5 of 5 File: DWPI Jun 23, 1990

DERWENT-ACC-NO: 1990-239045
DERWENT-WEEK: 200134

TITLE: Enzymatically active recombinant glucocerebrosidase - useful for treating Gauchers disease

INVENTOR: BARSOMIAN, G; BERGH, M ; RASMUSSEN, J

PATENT-ASSIGNEE: GENZYME CORP (GENZ)

PRIORITY-DATA: 1988US-0289589 (December 23, 1988), 1989US-0455507 (December 22, 1989), 1989WO-US05801 (December 22, 1989), 1991US-0748283 (August 21, 1991)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
CA 2339888 A1	June 23, 1990	E	000	C12N005/10
WO 9007573 A	July 12, 1990		000	
EP 401362 A	December 12, 1990		000	
CA 2006709 A	July 31, 1990		000	
JP 03503721 W	August 22, 1991		000	
US 5236838 A	August 17, 1993		021	C12N009/42
EP 401362 A4	September 11, 1991		000	
EP 401362 B1	May 29, 1996	E	021	C12N009/24
DE 68926569 E	July 4, 1996		000	C12N009/24
ES 2093642 T3	January 1, 1997		000	C12N009/24
JP 2893481 B2	May 24, 1999		019	C12N015/09

DESIGNATED-STATES: JP AT BE CH DE ES FR GB IT LI LU NL SE AT BE CH DE FR GB IT LI LU NL SE AT BE CH DE ES FR GB IT LI LU NL SE

CITED-DOCUMENTS:6.Jnl.Ref; US 4745051 ; 3.Jnl.Ref ; WO 8905850 ; 9.Jnl.Ref

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
CA 2339888A1	December 27, 1989	1989CA-2006709	Div ex
CA 2339888A1	December 27, 1989	1989CA-2339888	
EP 401362A	December 22, 1989	1990EP-0901476	
JP 03503721W	December 22, 1989	1990JP-0502257	
US 5236838A	December 23, 1988	1988US-0289589	CIP of
US 5236838A	December 22, 1989	1989US-0455507	Div ex
US 5236838A	August 21, 1991	1991US-0748283	
EP 401362A4		1990EP-0901476	
EP 401362B1	December 22, 1989	1989WO-US05801	
EP 401362B1	December 22, 1989	1990EP-0901476	
EP 401362B1		WO 9007573	Based on
DE 68926569E	December 22, 1989	1989DE-0626569	
DE 68926569E	December 22, 1989	1989WO-US05801	
DE 68926569E	December 22, 1989	1990EP-0901476	
DE 68926569E		EP 401362	Based on
DE 68926569E		WO 9007573	Based on
ES 2093642T3	December 22, 1989	1990EP-0901476	
ES 2093642T3		EP 401362	Based on
JP 2893481B2	December 22, 1989	1989WO-US05801	
JP 2893481B2	December 22, 1989	1990JP-0502257	
JP 2893481B2		JP 3503721	Previous Publ.
JP 2893481B2		WO 9007573	Based on

INT-CL (IPC): A01K 67/00; C12N 5/00; C12N 5/10; C12N 9/24; C12N 9/42; C12N 15/09; C12N 15/52; C12N 15/56; C12N 15/63; C12N 15/79; C12N 15/81; C12N 15/85

RELATED-ACC-NO: 1996-401555

ABSTRACTED-PUB-NO: EP 401362B
BASIC-ABSTRACT:

Recombinant enzymatically active glucocerebrosidase (I) produced by a eukaryotic cell is new. Also claimed is (I) comprising at least one exposed mannose residue, (I) being capable of binding with a human mannose receptor protein. A eukaryotic cell comprising nucleic acid encoding (I) is also claimed. The cell is pref. an insect or mammalian cell, esp. Chinese hamster ovary (CHO) cell.

(I) pref. comprises a carbohydrate moiety with 3-9 exposed mannose residues, pref. arranged in a Manz to Mang structure.

USE/ADVANTAGE - (I) is useful for treatment of Gaueher's disease using a standard enzyme replacement protocol. (I) is free from viral or bacterial agents commonly found in human tissues, e.g., placenta, the prior art source of the enzyme. (I) is secreted in large amts. from the cells in which it is produced into the surrounding medium, from which it is readily purified.

ABSTRACTED-PUB-NO: US 5236838A
EQUIVALENT-ABSTRACTS:

A Chinese hamster ovary (CHO) cell comprising nucleic acid encoding enzymatically active glucocerebrosidase, wherein said glucocerebrosidase is capable of specifically binding with a human mannose receptor protein.

Prodn. of enzymatically active glucocerebrosidase comprises introducing nucleic acid encoding human glucocerebrosidase into CHO cell, causing the cell to express and secrete the glucocerebrosidase into a culture medium and purifying the prod. from the culture medium.

The pH of the culture medium is kept at 6.5 to 7.7 pref. 6.6 to 6.8. The medium

contains oxygen in an amt. below about 50% saturation pref. between 20% and 30% saturation and sufficient to maintain the cells. The plasmid used to introduce the encoding nucleic acid is pref. e.g. pGB20 pGB37 and pGB42.

USE - To treat Gauche's disease.

WO 9007573A

CHOSEN-DRAWING: Dwg.2/10 Dwg.0/10 Dwg.0/10

DERWENT-CLASS: B04 D16 P14
CPI-CODES: B04-B02C3; B04-B04A3; B12-G02; D05-H03B; D05-H08; D05-H13;

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L3: Entry 5 of 5 File: DWPI Jun 23, 1990

DERWENT-ACC-NO: 1990-239045
DERWENT-WEEK: 200134

TITLE: Enzymatically active recombinant glucocerebrosidase - useful for treating Gauchers disease

ABEQ:
A Chinese hamster ovary (CHO) cell comprising nucleic acid encoding enzymatically active glucocerebrosidase, wherein said glucocerebrosidase is capable of specifically binding with a human mannose receptor protein.

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L3: Entry 4 of 5 File: USPT Aug 27, 1996

US-PAT-NO: 5549892
DOCUMENT-IDENTIFIER: US 5549892 A

TITLE: Enhanced in vivo uptake of glucocerebrosidase

DATE-ISSUED: August 27, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; BethAnn	Arlington	MA		
Hayes; Michael	Acton	MA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Genzyme Corporation	Cambridge	MA			02

APPL-NO: 8/ 080855
DATE FILED: June 21, 1993

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATION This application is a continuation-in-part of U.S. application Ser. No. 07/748,283, filed Aug. 21, 1991, now U.S. Pat. No. 5,236,838, a divisional application of U.S. application Ser. No. 455,507, filed Dec. 22, 1989, now abandoned, which was filed as a continuation-in-part of U.S. application Ser. No. 289,589, Dec. 23, 1988, now abandoned. The related applications are hereby incorporated by reference.

INT-CL: [6] A61K 38/47, C12N 9/42, C12N 15/56
US-CL-ISSUED: 424/94.61; 435/209, 536/232
US-CL-CURRENT: 424/94.61; 435/209, 536/23.2
FIELD-OF-SEARCH: 424/94.61, 536/23.2, 435/209

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4713339	December 1987	Levinson et al.	435/240.2

OTHER PUBLICATIONS

Tsuji, S. et al. (1986) "Nucleotide Sequence of cDNA Containing the Complete Coding Sequence for Human Lysosomal Glucocerebrosidase" The Journal of Biological Chemistry, 261(1):50-53.
Sorge, J. et al. (1985) "Molecular Cloning and Nucleotide Sequence of Human Glucocerebrosidase cDNA" Proc. Natl. Acad. Sci, USA, 82:7289-7293.
Furbish, F. S. et al (1981) "Uptake and Distribution of Placental Glucocerebrosidase in Rat Hepatic Cells and Effects of Sequential Deglycosylation" Biochimica et Biophysica Acta, 673:425-434.

Furbish, F. S. et al. (1977) "Enzyme replacement therapy in Gaucher's disease: Large-Scale purification of glucocerebrosidase suitable for human administration" Proc. Natl. Acad. Sci. USA 74(8) 3560-3563.
Brady, R. O. (1966) "The Sphingolipidoses" The New England Journal of Medicine, 275(6):312-317.
B. M. Martin et al. "Glycosylation and Processing of High Levels of Active . . . " DNA 7(2) 99-106 (Mar. 1988).
M. Bergh et al. "Heterologers Expression at Human Glucocerebrosidase . . . " Absts. Paper. Am. Chem. Soc. 199th Meet. BIOT 51 (Apr. 1990).
M. Bergh et al. "Processing and Glycosylation of Human Glucocerebrosidase . . . " Absts. Papers. Am. Chem. Soc. 200th Meet. BIOT 109 (Aug. 1990).
G. J. Murray et al. "Lectin-Specific Targeting at Lysosomal Enzymes . . . " Meth. in Enzymol 149:25-42 (1987).

ART-UNIT: 184
PRIMARY-EXAMINER: Wax; Robert A.
ASSISTANT-EXAMINER: Prouty; Rebecca
ATTY-AGENT-FIRM: Gosz; William G.

ABSTRACT:

A pharmaceutical composition comprising remodelled recombinant glucocerebrosidase (GCR) is described that provides a therapeutic effect at doses that are lower then those required using remodelled naturally occurring GCR. A method of treating patients with Gaucher's disease using remodelled recombinant GCR is also provided. In vivo uptake of exogenous molecules can be determined by extracting a mixture of cells from a subject, enriching the target cells in vitro, lysing the cells and determining the amount of exogenous molecules.

10 Claims, 2 Drawing figures

WEST

Generate Collection

L3: Entry 4 of 5 File: USPT Aug 27, 1996

US-PAT-NO: 5549892
DOCUMENT-IDENTIFIER: US 5549892 A

TITLE: Enhanced in vivo uptake of glucocerebrosidase

DATE-ISSUED: August 27, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; BethAnn	Arlington	MA		
Hayes; Michael	Acton	MA		

US-CL-CURRENT: 424/94.61; 435/209, 536/23.2

CLAIMS:

What is claimed is:
1. A pharmaceutical composition, comprising:
remodeled recombinant GCR, obtained from CHO cells, wherein the remodeled recombinant GCR has exposed mannose terminal residues on appended oligosaccharides, in an effective dosage suitable for significantly alleviating clinical symptoms of Gaucher's disease, such that the dose is substantially less than the effective dose using remodeled naturally occurring GCR.
2. The pharmaceutical composition of claim 1, wherein the recombinant GCR differs from naturally occurring GCR by having a histidine at amino acid number 495.
3. The pharmaceutical composition of claim 1, wherein the remodelled recombinant GCR has increased fucose compared to remodelled naturally occurring GCR.
4. The pharmaceutical composition of claim 1 wherein the remodelled recombinant GCR has increased N-acetyl glucosamine residues compared to remodelled naturally occurring GCR.
5. A method for treating a human subject having Gaucher's disease using exogenous GCR, comprising:
(a) providing a recombinant form of GCR obtained from CHO cells and capable of effectively targeting cells abnormally deficient in GCR, wherein the recombinant GCR has exposed terminal mannose residues on appended oligosaccharides;
(b) administering such form of the GCR to the subject in doses sufficient to achieve a therapeutic effect, each dose being dependent on the effective targeting of cells abnormally deficient in GCR; and each dose of such form of GCR being substantially less than the dose of naturally occurring GCR that would otherwise be administered in a similar manner to achieve the therapeutic effect.
6. A method according to claim 5, wherein the recombinant GCR differs from naturally occurring GCR by having a histidine at amino acid number 495.
7. A method according to claim 5, wherein the recombinant GCR has a carbohydrate moiety having increased fucose and N-acetylglucosamine residues compared to the naturally occurring forms of GCR.
8. A method according to claim 5, wherein the targeting capability in step (a) is determined in relation to the uptake by a population of target cells and the recombinant GCR has increased affinity for the target cells in comparison with that of naturally occurring GCR.
9. A method according to claim 8, wherein the cells at the target site are Kupffer cells in the liver.
10. A pharmaceutical composition for significantly alleviating clinical symptoms of Gaucher's disease comprising remodeled recombinant GCR obtained from CHO cells the remodeled recombinant GCR having an effective dosage that is substantially

less than the effective dosage for remodeled naturally occurring GCR.

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L3: Entry 3 of 5 File: USPT Jun 15, 1999

DOCUMENT-IDENTIFIER: US 5911983 A
TITLE: Gene therapy for Gaucher disease using retroviral vectors

BSPR:
The first of the two Gaucher disease treatments based on this strategy is allogeneic bone marrow transplantation, which results in the repopulation of affected tissues with enzyme-competent macrophages. See, Rappeport, J. M., et al., Birth Defects: Original Article Series 22,1:101 (1986). The second approach to treatment which has resulted in clinical improvement in Gaucher disease patients is macrophage-targeted enzyme replacement. This treatment takes advantage of naturally occurring mannose receptors on macrophages and the exposition of accessible mannose receptors in the oligosaccharides of glucocerebrosidase to efficiently deliver the enzyme to macrophages. See, Barranger, J. A., et al., Japanese J. of Inher. Met. Disease 51:45 (1989); Takasaki, S., et al., J. Biol. Chem. 259:10112 (1984); and Furbish, F. S., et al., Biochem. Biophys. Acta. 673:425 (1981). While both of these approaches to treating Gaucher disease are important because they provide some means of therapy where none previously existed, both approaches have significant limitations. Allogeneic bone marrow transplantation has associated with it morbidity and mortality risks that are unacceptable for many patients. Further, HLA matched bone marrow donors do not exist for the majority of patients. As for macrophage-targeted enzyme replacement, it is currently an expensive and life-long therapy; thus, it should be reserved for only the most severely ill patients.

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L3: Entry 1 of 5 File: USPT Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6210666 B1
TITLE: Truncated .alpha.-galactosidase A to treat fabry disease

DEPR:
Therapeutic approaches using enzyme replacement are under investigation for lysosomal storage diseases, including Fabry disease. Recent success in the therapy of Gaucher's disease using mannose-terminated (macrophage-targeted) human glucocerebrosidase has demonstrated that this approach is valid (N. W. Barton et al., Proc. Natl. Acad. Sci. USA, 87, 1913 (1990); N. W. Barton et al., N. Engl. J. Med., 324, 1464 (1991)). For Fabry disease, .alpha.-Gal A replacement using .alpha..sub.2 -macroglobulin as a transport vehicle has been suggested (A. R. Tsuji et al., J. Biochem., 115, 937 (1994)). As described above, removal of several residues from the C-terminal sequence of wild type .alpha.-Gal A resulted in a remarkable increase of its enzyme activity. Thus, these mutant enzymes can be used in replacement therapy, as has been done in insulin therapy using a C-terminal mutant (D. C. Howey et al., Diabetes, 43, 396 (1994)), and in the future, in gene therapy.

WEST

Generate Collection

L3: Entry 4 of 5 File: USPT Aug 27, 1996

DOCUMENT-IDENTIFIER: US 5549892 A
TITLE: Enhanced in vivo uptake of glucocerebrosidase

BSPR:
Unmodified glucocerebrosidase derived from natural sources is a glycoprotein with four carbohydrate chains. This protein does not target the phagocytic cells in the body and is therefore of limited therapeutic value. In developing the current therapy for Gaucher's disease, the terminal sugars on the carbohydrate chains of glucocerebrosidase are sequentially removed by treatment with three different glycosidases. This glycosidase treatment results in a glycoprotein whose terminal sugars consist of mannose residues. Since phagocytes have mannose receptors that recognize glycoproteins and glycopeptides with oligosaccharide chains that terminate in mannose residues, the carbohydrate remodeling of glucocerebrosidase has improved the targeting of the enzyme to these cells (Furbish et al., Biochem. Biophys. Acta 673:425, 1981)

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 NEWS  2  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload
 NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                  DWPI and DPCI
 NEWS 10  Aug 23  In-process records and more frequent updates now in
                  MEDLINE
 NEWS 11  Aug 23  PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
 NEWS 12  Aug 23  Adis Newsletters (ADISNEWS) now available on STN
 NEWS 13  Sep 17  IMSworld Pharmaceutical Company Directory name change
                  to PHARMASEARCH
 NEWS 14  Oct 09  Korean abstracts now included in Derwent World Patents
                  Index
 NEWS 15  Oct 09  Number of Derwent World Patents Index updates increased
 NEWS 16  Oct 15  Calculated properties now in the REGISTRY/ZREGISTRY File
 NEWS 17  Oct 22  Over 1 million reactions added to CASREACT
 NEWS 18  Oct 22  DGENE GETSIM has been improved
 NEWS 19  Oct 29  AAASD no longer available

 NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
               CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
               AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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=> s glucocerebrosidase
L1        4485 GLUCOCEREBROSIDASE

=> s l1 (10a)mannose
L2         133 L1 (10A) MANNOSE

=> s l1 (10a) high(3a) mannose
L3          22 L1 (10A) HIGH(3A) MANNOSE

=> s l1 (10a) gaucher
L4        1771 L1 (10A) GAUCHER

=> s l2 (10a) gaucher
L5          51 L2 (10A) GAUCHER

=> s l3 (10a)gaucher
L6           1 L3 (10A) GAUCHER

=> d

L6   ANSWER 1 OF 1  BIOSIS  COPYRIGHT 2001 BIOSIS
AN   1993:292150  BIOSIS
DN   PREV199345010275
TI   Treatment of neuronopathic (NP) Gaucher's disease (GD) with
     high dose mannose terminal glucocerebrosidase
     (M-GC.
AU   Abella, Esteban (1); Smietana, Susan; Bawle, Erawati; Moylan, Patricia;
     Richards, Debbie; Becker, Cristie; Ravindranath, Yaddanapudi
CS   (1) Dep. Pediatrics, Wayne State Univ., Detroit, MI
SO   Pediatric Research, (1993) Vol. 33, No. 4 PART 2, pp. 124A.
     Meeting Info.: 103rd Annual Meeting of the American Pediatric Society and
     62nd Annual Meeting of the Society for Pediatric Research Washington,
     D.C., USA May 3-6, 1993
     ISSN: 0031-3998.
DT   Conference
LA   English
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=> d ab

L6 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2001 BIOSIS

=> s l3 and purif?
L7 5 L3 AND PURIF?

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 2 DUP REM L7 (3 DUPLICATES REMOVED)

=> d 1,2

L8 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
AN 96030524 EMBASE
DN 1996030524
TI [Enzyme replacement: A new therapeutic approach in Gaucher disease].
NEUES THERAPIEKONZEPT BEI M. GAUCHER. ENZYM-SUBSTITUTION.
AU Beck M.
CS Universitats-Kinderklinik, Langenbeckstrasse 1,55101 Mainz, Germany
SO Sozialpadiatrie und Kinderarztliche Praxis, (1996) 18/1 (22+24-25).
ISSN: 0945-7712 CODEN: SKIPEJ
CY Germany
DT Journal; (Short Survey)
FS 007 Pediatrics and Pediatric Surgery
022 Human Genetics
037 Drug Literature Index
LA German
SL German; English

L8 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AN 82068152 MEDLINE
DN 82068152 PubMed ID: 7306020
TI Studies in vivo of the tissue uptake, cellular distribution and catabolic turnover of exogenous glucocerebrosidase in rat.
AU Morrone S; Pentchev P G; Baynes J; Thorpe S
NC AM 19971 (NIADDK)
AM 25373 (NIADDK)
SO BIOCHEMICAL JOURNAL, (1981 Mar 15) 194 (3) 733-42.
Journal code: 9YO; 2984726R. ISSN: 0264-6021.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198201
ED Entered STN: 19900316
Last Updated on STN: 19970203
Entered Medline: 19820109

=> d 1, 2 ab

L8 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
AB Gaucher's disease is the most prevalent sphingolipidosis; it is due to a genetic deficiency of the enzyme glucocerebrosidase that is reponsible for the degradation of glucocerebroside. Due to the reduced enzyme activity glucocerebroside accumulates in the reticulo-endothelial system causing a multisystem disorder with massive enlargement of the liver and spleen, subsequent pancytopenia, bleeding diathesis and abdominal pain. The skeletal involvement may lead to pathological fractures and deformities. Until recently treatment for the most symptomatic patients was supportive with blood transfusions, total or partial splenectomy. Because of severe osteonecrosis of the femoral head, in many cases joint replacement surgery became necessary. In selected patients with rapidly progressing disease, improvement was achievable, but at high risk, through bone marrow transplantation or liver transplantation. Early attempts to treat the patients by exogenous administration of the .beta.-glucocerebrosidase

failed as the enzyme did not accumulate in the storage cells. But, if the enzyme that had been **purified** from human placenta was modified to expose **mannose** residues, a **high** activity inside the macrophages could be obtained. This **glucocerebrosidase** preparation markedly improves the clinical and biochemical abnormalities in patients with type Gaucher's disease.

L8 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AB The kinetics of plasma clearance of highly **purified** human placental glucocerebrosidase in rats were biphasic with 75% of the infused dose showing a rapid clearance (t1/2 = 11 min) and the remaining 25% a considerably lower rate (t1/2 = 60 min). The majority of the enzyme (60%) was taken up by the liver. Although saturation kinetics for the clearance or uptake were not observed, the very high hepatic endocytic index (217 microliter/min) of glucocerebrosidase uptake indicated that liver uptake was mediated by an adsorptive endocytic process. Analysis of the cellular distribution of recovered glucocerebrosidase revealed predominantly parenchymal cell uptake with 38% of the exogenous enzyme in hepatocytes and only 2% in sinusoidal cells. **High-mannose** glycoproteins blocked hepatocyte and sinusoidal cell uptake of **glucocerebrosidase** equally. Kinetic experiments failed to demonstrate a transfer or shuttle of exogenous glucocerebrosidase from sinusoidal cells to hepatocytes. The possibility was raised that uptake of enzyme by the liver may be mediated by a common receptor that functions in both hepatocytes and sinusoidal cells. The catabolic turnover of exogenous glucocerebrosidase in rat liver was biphasic and the rate of decline was similar in hepatocytes and sinusoidal cells.

=> dup rem l3
PROCESSING COMPLETED FOR L3
L9 6 DUP REM L3 (16 DUPLICATES REMOVED)

=> d 1-6

L9 ANSWER 1 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
AN 96030524 EMBASE
DN 1996030524
TI [Enzyme replacement: A new therapeutic approach in Gaucher disease]. NEUES THERAPIEKONZEPT BEI M. GAUCHER. ENZYM-SUBSTITUTION.
AU Beck M.
CS Universitats-Kinderklinik, Langenbeckstrasse 1,55101 Mainz, Germany
SO Sozialpadiatrie und Kinderarztliche Praxis, (1996) 18/1 (22+24-25). ISSN: 0945-7712 CODEN: SKIPEJ
CY Germany
DT Journal; (Short Survey)
FS 007 Pediatrics and Pediatric Surgery
022 Human Genetics
037 Drug Literature Index
LA German
SL German; English

L9 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:292150 BIOSIS
DN PREV199345010275
TI Treatment of neuronopathic (NP) Gaucher's disease (GD) with **high** dose **mannose** terminal **glucocerebrosidase** (M-GC.
AU Abella, Esteban (1); Smietana, Susan; Bawle, Erawati; Moylan, Patricia; Richards, Debbie; Becker, Cristie; Ravindranath, Yaddanapudi
CS (1) Dep. Pediatrics, Wayne State Univ., Detroit, MI
SO Pediatric Research, (1993) Vol. 33, No. 4 PART 2, pp. 124A. Meeting Info.: 103rd Annual Meeting of the American Pediatric Society and 62nd Annual Meeting of the Society for Pediatric Research Washington, D.C., USA May 3-6, 1993 ISSN: 0031-3998.
DT Conference
LA English

L9 ANSWER 3 OF 6 MEDLINE DUPLICATE 2

AN 90361052 MEDLINE
DN 90361052 PubMed ID: 2143986
TI Function of oligosaccharide modification in glucocerebrosidase, a membrane-associated lysosomal hydrolase.
AU Van Weely S; Aerts J M; Van Leeuwen M B; Heikoop J C; Donker-Koopman W E; Barranger J A; Tager J M; Schram A W
CS E. C. Slater Institute for Biochemical Research, University of Amsterdam, The Netherlands.
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1990 Aug 17) 191 (3) 669-77.
Journal code: EMZ; 0107600. ISSN: 0014-2956.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199010
ED Entered STN: 19901109
Last Updated on STN: 19901109
Entered Medline: 19901004

L9 ANSWER 4 OF 6 MEDLINE DUPLICATE 3
AN 88195783 MEDLINE
DN 88195783 PubMed ID: 3282855
TI Glycosylation and processing of high levels of active human glucocerebrosidase in invertebrate cells using a baculovirus expression vector.
AU Martin B M; Tsuji S; LaMarca M E; Maysak K; Eliason W; Ginns E I
CS Molecular Neurogenetics Section, National Institute of Mental Helath, Bethesda, MD 20892.
SO DNA, (1988 Mar) 7 (2) 99-106.
Journal code: EAW; 8302432. ISSN: 0198-0238.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198806
ED Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880609

L9 ANSWER 5 OF 6 MEDLINE DUPLICATE 4
AN 86033922 MEDLINE
DN 86033922 PubMed ID: 3932353
TI Biosynthesis of the lysosomal enzyme glucocerebrosidase.
AU Erickson A H; Ginns E I; Barranger J A
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1985 Nov 15) 260 (26) 14319-24.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198512
ED Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19851213

L9 ANSWER 6 OF 6 MEDLINE DUPLICATE 5
AN 82068152 MEDLINE
DN 82068152 PubMed ID: 7306020
TI Studies in vivo of the tissue uptake, cellular distribution and catabolic turnover of exogenous glucocerebrosidase in rat.
AU Morrone S; Pentchev P G; Baynes J; Thorpe S
NC AM 19971 (NIADDK)
AM 25373 (NIADDK)
SO BIOCHEMICAL JOURNAL, (1981 Mar 15) 194 (3) 733-42.
Journal code: 9YO; 2984726R. ISSN: 0264-6021.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 198201
ED Entered STN: 19900316
Last Updated on STN: 19970203
Entered Medline: 19820109

=> d 3, 4 ab

L9 ANSWER 3 OF 6 MEDLINE DUPLICATE 2
AB The nature and function of oligosaccharide modification in glucocerebrosidase, a membrane-associated lysosomal hydrolase, have been investigated in cultured human skin fibroblasts. **Glucocerebrosidase** is synthesised as a 62.5-kDa precursor with **high-mannose**-type oligosaccharide chains and an apparent native isoelectric point of 6.0-7.0. Subsequent processing of the oligosaccharide moieties to sialylated complex-type structures results in formation of 65-68-kDa forms of the enzyme with apparent native isoelectric points of 4.3-5.0. These forms are transported to lysosomes and subsequently modified by the sequential action of lysosomal exoglycosidases, finally resulting in a 59-kDa form with an isoelectric point near neutrality. The existence of oligosaccharide modification of the enzyme in the lysosomes is illustrated by the accumulation of different intermediate forms of glucocerebrosidase in mutant cell lines deficient in lysosomal exoglycosidases. The enzyme does not undergo proteolytic modification during maturation. The possible physiological relevance of the oligosaccharide modification of glucocerebrosidase in the lysosomes was investigated by studying the properties of the enzyme in fibroblasts deficient in lysosomal exoglycosidases, and also the properties of homogeneous pure glucocerebrosidase from placenta, modified in the oligosaccharide moieties by digestion in vitro with glycosidases. Modification of the oligosaccharide moieties of glucocerebrosidase had no significant effect on the catalytic activity of the enzyme as measured with either artificial or natural substrates in the presence of artificial or natural activators. There was also no effect of modification of the oligosaccharide chains on the intracellular stability of the enzyme or on its apparent hydrophobicity. We conclude that oligosaccharide modification of glucocerebrosidase in the lysosomes simply reflects further maturation of the enzyme in the lysosome and is of no importance to its function.

L9 ANSWER 4 OF 6 MEDLINE DUPLICATE 3
AB A human cDNA containing the complete coding region for the lysosomal glycoprotein glucocerebrosidase (EC 3.2.1.45) was introduced into the genome of Autographa californica nuclear polyhedrosis virus downstream from the polyhedrin promoter. Infection of Spodoptera frugiperda cells (SF9) with recombinant virus produced high levels of glucocerebrosidase, 40% of which was in the culture medium. The amino-terminal amino acid sequence of the recombinantly produced enzyme was identical to that of mature, human placental glucocerebrosidase, demonstrating that the signal sequence of the human preenzyme was recognized and appropriately removed in the SF9 invertebrate cells. The glucocerebrosidase in both the culture supernatant and SF9 cell pellet was glycosylated and contained, in part, high mannose oligosaccharide. These results demonstrate that insect cells can be used to produce abundant quantities of active mature human **glucocerebrosidase** that contains **high mannose** oligosaccharide as a consequence of post-translational processing.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	32.81	32.96

FILE 'STNGUIDE' ENTERED AT 19:32:40 ON 07 NOV 2001

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 26, 2001 (20011026/UP).

```
=> s l1 (10a) inhibitor
            0 GLUCOCEREBROSIDASE
            0 INHIBITOR
L10         0 L1 (10A) INHIBITOR

=> fil .eliz
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.00      32.96

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=> s l1 (10a) inhibitor
L11         104 L1 (10A) INHIBITOR

=> s l1 (10a) (swainsonine or kifunensine)
L12           4 L1 (10A) (SWAINSONINE OR KIFUNENSINE)

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13           1 DUP REM L12 (3 DUPLICATES REMOVED)

=> d

L13  ANSWER 1 OF 1     MEDLINE                          DUPLICATE 1
AN   87100162     MEDLINE
DN   87100162   PubMed ID: 2948505
TI   Efficient routing of glucocerebrosidase to lysosomes requires complex
     oligosaccharide chain formation.
AU   Aerts J M; Brul S; Donker-Koopman W E; van Weely S; Murray G J; Barranger
     J A; Tager J M; Schram A W
SO   BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1986 Dec 15) 141 (2)
     452-8.
```

Journal code: 9Y8; 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198702
ED Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19870202

=> d ab

L13 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AB The biosynthesis and intracellular transport of the membrane-associated lysosomal enzyme glucocerebrosidase was studied in the monoblast cell line U937. Addition to the cultures of the oligosaccharide trimming inhibitors **swainsonine** or deoxymannojirimycin led to an increased intracellular activity of **glucocerebrosidase**. This was due to prevention of the lysosomal degradation of the enzyme. When homogenates of control cells were fractionated on Percoll gradients glucocerebrosidase, like beta-hexosaminidase, was distributed in two peaks, one at low density and one at high density. When homogenates of cells cultured in the presence of oligosaccharide-trimming inhibitors were fractionated beta-hexosaminidase was still distributed in two peaks but glucocerebrosidase was found mainly in low density fractions also containing galactosyltransferase activity. It is concluded that complex type oligosaccharide chain formation is required for efficient routing of glucocerebrosidase to the lysosomes in U937 cells.

=> s l1 (10a) (mannosidase)(3a) inhibitor
L14 0 L1 (10A) (MANNOSIDASE)(3A) INHIBITOR

=> s l1 (10a) (mannosidase)
L15 0 L1 (10A) (MANNOSIDASE)

=> s l1 (10a)(deoxymannojirimycin or mannostatin or 6-deoxy-dim or 6-deoxy-6-fluoro-dim)
9 FILES SEARCHED...
L16 4 L1 (10A)(DEOXYMANNOJIRIMYCIN OR MANNOSTATIN OR 6-DEOXY-DIM OR 6-DEOXY-6-FLUORO-DIM)

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17 1 DUP REM L16 (3 DUPLICATES REMOVED)

=> d

L17 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AN 87100162 MEDLINE
DN 87100162 PubMed ID: 2948505
TI Efficient routing of glucocerebrosidase to lysosomes requires complex oligosaccharide chain formation.
AU Aerts J M; Brul S; Donker-Koopman W E; van Weely S; Murray G J; Barranger J A; Tager J M; Schram A W
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1986 Dec 15) 141 (2) 452-8.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198702
ED Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19870202

=> d ab

L17 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AB The biosynthesis and intracellular transport of the membrane-associated lysosomal enzyme glucocerebrosidase was studied in the monoblast cell line U937. Addition to the cultures of the oligosaccharide trimming inhibitors swainsonine or **deoxymannojirimycin** led to an increased intracellular activity of **glucocerebrosidase**. This was due to prevention of the lysosomal degradation of the enzyme. When homogenates of control cells were fractionated on Percoll gradients glucocerebrosidase, like beta-hexosaminidase, was distributed in two peaks, one at low density and one at high density. When homogenates of cells cultured in the presence of oligosaccharide trimming inhibitors were fractionated beta-hexosaminidase was still distributed in two peaks but glucocerebrosidase was found mainly in low density fractions also containing galactosyltransferase activity. It is concluded that complex type oligosaccharide chain formation is required for efficient routing of glucocerebrosidase to the lysosomes in U937 cells.

=> s kinoshita, ?/AU
L18 46977 KINOSHITA, ?/AU

=> S L1 AND L18
L19 7 L1 AND L18

=> DUP REM L19
PROCESSING COMPLETED FOR L19
L20 1 DUP REM L19 (6 DUPLICATES REMOVED)

=> D

L20 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AN 96061066 MEDLINE
DN 96061066 PubMed ID: 7576080
TI Position of the sulfhydryl group and the disulfide bonds of human **glucocerebrosidase**.
AU Lee Y; **Kinoshita H**; Radke G; Weiler S; Barranger J A; Tomich J M
CS Department of Pediatrics, University of Southern California Medical School, Childrens Hospital of Los Angeles, California 90027, USA.
SO JOURNAL OF PROTEIN CHEMISTRY, (1995 Apr) 14 (3) 127-37.
Journal code: AEJ; 8217321. ISSN: 0277-8033.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199511
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951128

=> D AB

L20 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AB Purified human **glucocerebrosidase** isolated from placenta was modified with [14C]-iodoacetic acid without reduction and digested with both protease-V8 at pH 4.0 followed by alpha-chymotrypsin at pH 7.5. The majority of radioactivity was found in a peptide that contained the [14C]-carboxymethylated-cysteine identified as CM-Cys18. Direct sequencing of the N-terminus of the intact labeled protein confirmed the modification of Cys18. For identification of disulfide bond-containing peptides, another portion of **glucocerebrosidase** was alkylated with nonlabeled iodoacetic acid and then digested with protease V8 and alpha-chymotrypsin as before. Twenty-eight HPLC fragments were collected. These purified peaks were then reduced with beta-mercaptoethanol followed by S-carboxymethylation with [14C]-iodoacetic acid. Three peptides among these 28 peptides generated two radioactive daughter peptides. These peptides were sequenced and the position of the radioactive CM-cysteines identified. The locations of these disulfides are Cys4-Cys16,

Cys23-Cys342, and Cys126-Cy[redacted]8. Attempts to reproduce the f[redacted] sulfhydryl labeling experiments using the **glucocerebrosidase** isolated from Ceredase proved unsuccessful. No label was incorporated by this enzyme prior to reduction. This result suggests that the form of the protein used in the clinic differs from the native protein.

```
=> S PRASHSANT, ?/AU
L21           0 PRASHSANT, ?/AU

=> S BOROWSKI, ?/AU
L22        3335 BOROWSKI, ?/AU

=> S L1 AND L22
L23           0 L1 AND L22

=> S FRANCIS-DANIEL, ?/AU
L24          11 FRANCIS-DANIEL, ?/AU

=> S L1 AND L24
L25           0 L1 AND L24

=> DIS HIS

     (FILE 'HOME' ENTERED AT 19:18:07 ON 07 NOV 2001)

     FILE 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS,
     NTIS, ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 19:18:19 ON 07 NOV 2001
L1          4485 S GLUCOCEREBROSIDASE
L2           133 S L1 (10A)MANNOSE
L3            22 S L1 (10A) HIGH(3A) MANNOSE
L4          1771 S L1 (10A) GAUCHER
L5            51 S L2 (10A) GAUCHER
L6             1 S L3 (10A)GAUCHER
L7             5 S L3 AND PURIF?
L8             2 DUP REM L7 (3 DUPLICATES REMOVED)
L9             6 DUP REM L3 (16 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 19:32:40 ON 07 NOV 2001
L10            0 S L1 (10A) INHIBITOR

     FILE 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS,
     NTIS, ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 19:35:26 ON 07 NOV 2001
L11          104 S L1 (10A) INHIBITOR
L12            4 S L1 (10A) (SWAINSONINE OR KIFUNENSINE)
L13            1 DUP REM L12 (3 DUPLICATES REMOVED)
L14            0 S L1 (10A) (MANNOSIDASE)(3A) INHIBITOR
L15            0 S L1 (10A) (MANNOSIDASE)
L16            4 S L1 (10A)(DEOXYMANNOJIRIMYCIN OR MANNOSTATIN OR 6-DEOXY-DIM O
L17            1 DUP REM L16 (3 DUPLICATES REMOVED)
L18        46977 S KINOSHITA, ?/AU
L19            7 S L1 AND L18
L20            1 DUP REM L19 (6 DUPLICATES REMOVED)
L21            0 S PRASHSANT, ?/AU
L22         3335 S BOROWSKI, ?/AU
L23            0 S L1 AND L22
L24           11 S FRANCIS-DANIEL, ?/AU
L25            0 S L1 AND L24

=> LOG H
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY     SESSION
FULL ESTIMATED COST                              27.75       60.71

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STN INTERNATIONAL SESSION SUSPENDED AT 19:48:21 ON 07 NOV 2001
Connection closed by remote host
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